TLR4 Signaling via NANOG Cooperates With STAT3 to Activate Twist1 and Promote Formation of Tumor-Initiating Stem-Like Cells in Livers of Mice.

Journal: Gastroenterology

Publication Year: 2016

Authors: Dinesh Babu Uthaya Kumar, Chia-Lin Chen, Jian-Chang Liu, Douglas E Feldman, Linda S Sher, Samuel French, Joseph DiNorcia, Samuel W French, Bita V Naini, Sunhawit Junrungsee, Vatche Garen Agopian, Ali Zarrinpar, Keigo Machida

PubMed link: 26582088

Funding Grants: CIRM Stem Cell Biology Training Program

Public Summary:
Chia-Lin Chen, a CIRM predoctoral fellow demonstrated Nanog cooperates with an essential pluripotent signal pathway to activate the epithelial-mesenchymal transition, resulting in formation of cancer stem cells and tumorigenesis.

Scientific Abstract:
BACKGROUND & AIMS: Obesity and alcohol consumption contribute to steatohepatitis, which increases the risk for hepatitis C virus (HCV)-associated hepatocellular carcinomas (HCCs). Mouse hepatocytes that express HCV-NS5A in liver up-regulate the expression of Toll-like receptor 4 (TLR4), and develop liver tumors containing tumor-initiating stem-like cells (TICs) that express NANOG. We investigated whether the TLR4 signals to NANOG to promote the development of TICs and tumorigenesis in mice placed on a Western diet high in cholesterol and saturated fat (HCFD). METHODS: We expressed HCV-NS5A from a transgene (NS5A Tg) in Tlr4-/- (C57Bl6/10ScN), and wild-type control mice. Mice were fed a HCFD for 12 months. TICs were identified and isolated based on being CD133+, CD49f+, and CD45-. We obtained 142 paraffin-embedded sections of different stage HCCs and adjacent nontumor areas from the same patients, and performed gene expression, immunofluorescence, and immunohistochemical analyses. RESULTS: A higher proportion of NS5A Tg mice developed liver tumors (39%) than mice that did not express HCV NS5A after the HCFD (6%); only 9% of Tlr4-/- NS5A Tg mice fed HCFD developed liver tumors. Livers from NS5A Tg mice fed the HCFD had increased levels of TLR4, NANOG, phosphorylated signal transducer and activator of transcription (pSTAT3), and TWIST1 proteins, and increases in Tlr4, Nanog, Stat3, and Twist1 messenger RNAs. In TICs from NS5A Tg mice, NANOG and pSTAT3 directly interact to activate expression of Twist1. Levels of TLR4, NANOG, pSTAT3, and TWIST were increased in HCC compared with nontumor tissues from patients. CONCLUSIONS: HCFD and HCV-NS5A together stimulated TLR4-NANOG and the leptin receptor (OB-R)-pSTAT3 signaling pathways, resulting in liver tumorigenesis through an exaggerated mesenchymal phenotype with prominent Twist1-expressing TICs.